PATENT

Attorney Docket No. 02481.1403-02

L. TUCK #28 10/6/99 1633

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Ulrich STACHE et al.

Serial No.: 08/897,455

Group Art Unit: 1616

Filed: July 22, 1997

Examiner: B. Badio

For: CORTICOID-17, 21-DICARBOXYLIC ESTERS AND CORTICOSTEROID 17-CARBOXYLIC ESTER 21-CARBONIC ESTERS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICALS CONTAINING THESE COMPOUNDS

BOX AF

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

In support of the Notice of Appeal filed on April 5, 1999, appellants present in triplicate their appeal brief accompanied by a check in the amount of $300.00 for the fee under 37 C.F.R. § 1.17(c). The period for response has been extended to October 5, 1999, by the Petition for Extension of Time and corresponding fee filed with this brief.

REAL PARTY IN INTEREST

Hoechst Aktiengesellschaft is the assignee of record. As presently advised, the successor to that company, Hoechst Marion Roussel Deutschland GmbH, is the real party in interest.

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RELATED APPEALS AND INTERFERENCES

The appellants, the appellants' legal representatives, and the assignee of record are presently unaware of any other appeal or interference that will directly affect or be directly affected by or have a bearing on the board's decision in this appeal.

STATUS OF CLAIMS

Claims 1, 3-5 and 7-10 are pending in this application. Claim 3 has been withdrawn from consideration, and claims 1, 4-5, and 7-10 are rejected and appealed. In response to a restriction requirement imposed under 35 U.S.C. § 121, appellants elected claims directed to compounds, compositions, and a method of use. Further, in response to an election of species requirement, appellants elected the compound of Example 6 as the single disclosed species. Claim 3, directed to a method of making the compounds of the invention, was the single non-elected claim and was withdrawn from consideration. In the Office action dated June 16, 1998 (Paper No. 20), the Examiner stated that process claims reciting compounds of the same scope as the allowed compounds would be rejoined for examination once the compound claims were found allowable. Appellants will therefore amend claim 3 as necessary upon allowance of the compound claims.

The Appendix to this brief contains a copy of all claims pending in this application.

STATUS OF AMENDMENTS

Claim 7 was amended for a second time and claims 9-10 were added in the Amendment After Final dated March 1, 1999. In the Advisory action dated March 19, 1999 (Paper No. 25), the Examiner indicated that those amendments would be entered upon the filing of the Notice of Appeal and Appeal Brief. Twice amended claim 7 and additional claims 9-10 are therefore properly pending for this appeal.

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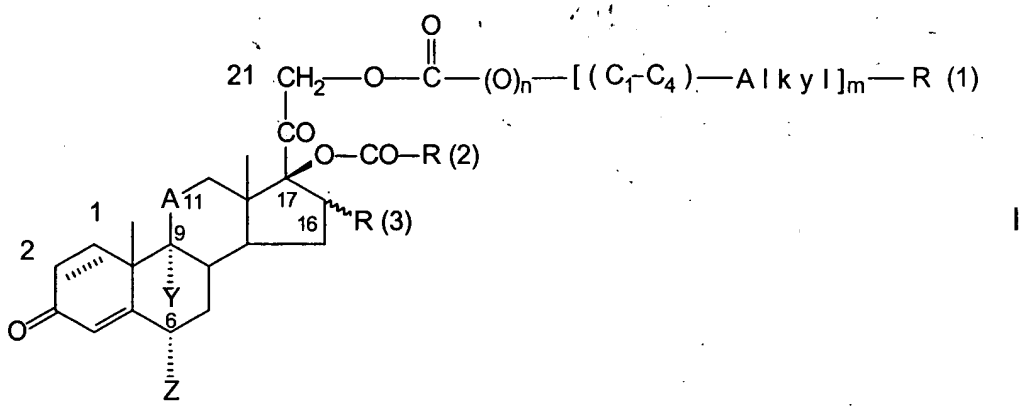
SUMMARY OF THE INVENTION

The present invention relates to particular corticoid 17,21-dicarboxylic esters or corticosteroid 17-carboxylic ester 21-carbonic esters, pharmaceutical compositions containing them, a method of using them, and a method of preparing them. (Specification at page 1, lines numbered 3-6). The invention as defined in claim 1 is directed to a corticoid 17,21-dicarboxylic ester or corticosteroid 17-carboxylic ester 21-carbonic ester of the formula I:



I

in which:

A is CHOH and CHCl in arbitrary steric arrangement, CH_2, C=O or 9(11) double bond (specification at page 1, lines numbered 7-12),

Y is hydrogen, fluorine or chlorine (specification at page 1, line number 13),

Z is hydrogen, fluorine or methyl (specification at page 1, line number 14),

R(1) is unsubstituted phenyl or phenyl substituted by one to three substituents selected from the group consisting of methoxy, chlorine, fluorine, methyl, trifluoromethyl, acetamino, acetaminomethyl, t-butoxy, t-butyl, 3,4-methylenedioxy, BOC-amino, amino and dimethylamino (specification at page 1, line number 15 and page 65, lines numbered 11-21),

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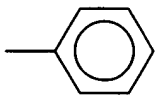
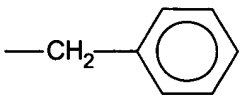
$(C_1$-$C_4)$-alkyl is

saturated, branched by further alkyl groups (specification at page 1, lines numbered 17-20),

n is zero (specification at page 1, line number 21)

m is 1 (specification at page 1, line number 22),

R(2) is linear or branched $(C_1$-$C_8)$-alkyl,  or  ,

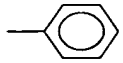
(specification at page 1, line number 23 to page 2, line number 1)

R(3) is hydrogen or α- or β-methyl (specification at page 2, line number 2).

Non-elected claim 3 depends from claim 1 and recites a process for preparing a compound of the invention. As explained above, the Examiner stated that process claims reciting compounds of the same scope as the allowed compounds would be rejoined for examination once the compound claims were found allowable. Claim 3 is supported in the specification at page 2, line number 9 to page 4, line number 11.

Claim 4 depends from claim 1 and is directed to a pharmaceutical composition for treating dermatoses containing an effective amount of a compound of the invention together with a pharmaceutically acceptable additive. Claim 4 is supported in the specification at page 13, lines numbered 20-33.

Claim 5 also depends from claim 1 and recites a method for treating dermatoses which comprises applying to skin in need of such treatment an effective amount of a compound of the invention together with a pharmaceutically acceptable additive. Claim 5 is supported in the specification at page 13, lines numbered 20-33.

Claim 7 depends from claim 1 and further defines the substituent R(2) in the formula I as  . Support for claim 7 appears in the specification at page 1, line number 23 to page 2, line number 1.

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Claim 8 depends from claim 4 and recites a pharmaceutical composition for treating dermatoses which are inflammatory and allergic. Claim 8 is supported in the specification at page 13, lines numbered 20-30.

Lastly, claims 9 and 10 depend from claim 1 and further define the substituents A, Y, Z, (C_1-C_4)-alkyl, R(1), R(2), and R(3) in the formula I. Claims 9 and 10 are supported in the specification by Examples 23 and 59.

ISSUES

I. Whether claims 1, 4-5, and 7-10 are rendered obvious under 35 U.S.C. § 103(a) by U.S. Patent No. 4,655,971 to Page et al.

II. Whether claims 1,4-5, and 7-10 are rendered obvious under 35 U.S.C. § 103(a) by U.S. Patent No. 4,645,763 to Annen et al.

III. Whether claim 7 is indefinite under 35 U.S.C. § 112, second paragraph.

GROUPING OF CLAIMS

Claims 1, 4-5, and 7-8 stand or fall together.

Claims 9 and 10 each stand alone.

ARGUMENT

I. Rejection Of Claims 1, 4-5, And 7-10 Under 35 U.S.C. § 103(a) Over Page et al.

A. The Examiner's Rejection.

Claims 1, 4-5, and 7-10 are rejected as obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 4,655,971 to Page et al. ("Page"). The Examiner states that Page teaches 17, 21-dicarboxylic esters of 4-pregnen-3,20-diones having either an oxo or a hydroxy group in the 11- position. The Examiner further asserts that the Page compounds contain substituents "similar" to the instant claims in the 6, 9, and 16 positions, and that they may contain a double bond in the 1 position. The Examiner also notes that Page teaches the

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use of the compounds in pharmaceutical compositions for the treatment of corticosteroid-responsive dermatosis.

The Examiner particularly emphasizes Page's disclosure of betamethasone-17-valerate-21-acetate and betamethasone-17-benzoate in Examples 9 and 19, respectively. Although conceding that those two compounds differ from the present compounds by having an acetate or hydroxyl in the 21- position, the Examiner nonetheless asserts that Page teaches an equivalence between a hydroxyl group and an acyl group in the 21-position, and an equivalence between acyl groups having an alkyl and an aralkyl moiety. The Examiner concludes that it would therefore have been obvious to modify the Page compounds of Examples 9 and 19 by replacing the acetate or hydroxyl groups in the 21-position with an aralkyl acyl group.

B. The Examiner Has Not Established A *Prima Facie* Case Of Obviousness.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based on the prior art. See In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). To establish a *prima facie* case of obviousness, the Examiner must identify some suggestion or motivation in the prior art to modify the reference to arrive at the claimed invention. See MPEP § 2143; In re Lalu, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). The Examiner has failed to establish a *prima facie* case of obviousness in this instance, and the rejection must therefore be reversed.

1. The Prior Art Did Not Motivate One Skilled In The Art To Derive The Claimed Invention

The patent relied upon by the Examiner, Page, discloses a process for the preparation of steroidal esters of the following formula:

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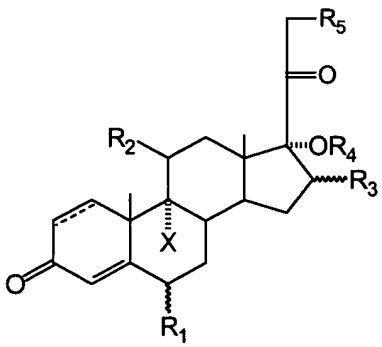

where the substituents R_1 to R_5 and X have the values set forth in the Page disclosure at col. 1, lines 32-55. The R_5 substituent of Page corresponds generally to the portion of the side chain in the 21- position of the presently claimed compounds beginning with the oxygen that follows the CH_2 group. This portion of the appellants' claimed compound reduces to -O-CO-[(C_1-C_4)-alkyl]-phenyl, with the phenyl being unsubstituted or substituted by one of the radicals recited in claim 1.

Focusing on the 21- position region of the claimed compounds alone, it is apparent that Page would not have motivated one skilled in the art to derive the claimed compounds having the -O-CO-[(C_1-C_4)-alkyl]-phenyl substituent. This is because such a derivation of the compounds could only have been made by an unguided simultaneous selection of a high number of independent variables from the Page disclosure. For example, following the various definitions of the substituents at col. 1, lines 32-55 of Page, one skilled in the art must have defined R_5 as R_6 (instead of as a hydroxyl group), R_6 must have been defined as OR_7 (instead of as a hydrogen or as one or two halogen atom substituents), where R_7 is an acyl group of the formula R'CO, and R' must have been defined as an aralkyl group of 7 to 8 carbon atoms (instead of a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group). There is no teaching or suggestion in Page or in the prior art as a whole to adopt these very specific combinations of substituents.

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The present situation is therefore analogous to the obviousness issues decided in In re Baird, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994) and In re Jones, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). In Baird, the applicant claimed a flash fusible toner comprising a binder resin which was a bisphenol A polyester containing an aliphatic dicarboxylic acid selected from succinic acid, glutaric acid, and adipic acid. The Examiner rejected the claim as obvious over a patent to Knapp, which disclosed esterification of diphenol compounds and dicarboxylic acids. Recognizing that bisphenol A could have been derived when specific variables were chosen from the Knapp disclosure, the Examiner reasoned that the claimed compound "may be easily derived from the generic formula of the diphenol in Knapp and all the motivation the worker of ordinary skill in the art needs to arrive at the particular polyester of the instant claim is to follow that formula." Id. at 1551. This rejection was upheld by the Board, but the Federal Circuit reversed.

The Baird court first noted that "[t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." Id. at 1552. Instead, the prior art must suggest the compound. Id. at 1552. In light of this test for obviousness, the court noted that "[w]hile the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables." Id. Apart from the generic disclosure in Knapp, the court also noted that the 15 specific diphenol compounds disclosed in Knapp were more complex than bisphenol A, rendering the Knapp disclosure as actually teaching away from the bisphenol A compound claimed by the applicants. Id. ("Indeed, Knapp appears to teach away from the selection of bisphenol A by focusing on more complex diphenols."). The court therefore ultimately concluded that the applicants had claimed a compound that was not taught or suggested by Knapp.

Similarly, in In re Jones, 21 U.S.P.Q.2d 1941, the applicant claimed a particular salt of the acid known as "dicamba." The Examiner rejected this claim over a patent to Richter,

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which disclosed a genus of salt forms of dicamba that encompassed the particular salt form claimed by Jones. In addition to its generic disclosure, Richter disclosed specific compounds that either lacked an ether linkage in the salt that was claimed by the applicant, or, if it did disclose such a linkage, the compound was cyclic, instead of acyclic as claimed. Id. at 1943. Noting the lack of guidance in Richter's generic disclosure to select the particular salt form claimed by Jones, and the dissimilarities between the particular examples of Richter from the claimed compound, the court held that Richter did not render the claimed compound obvious. Id.

The Examiner argues in the present case that In re Baird is not applicable to appellants' claims, contending that the pending claims encompass numerous compounds, and the claim on appeal in Baird was directed only to a specific compound. Section 2144.08 of the MPEP, however, relies on In re Baird in formulating the examination procedures for determining the obviousness of either a single species *or a subgenus* of a prior art disclosure. The Examiner's interpretation of In re Baird as applicable only to claims directed to a single species compound is therefore at odds with the interpretation of In re Baird given by the Patent and Trademark Office. Apart from the Patent Office's interpretation, it would appear that the discussion in In re Baird concerning the motivation to arrive at the invention would be equally pertinent to the selection of a subgenus in any event. Appellants should therefore be entitled to rely on the reasoning of In re Baird for all the pending claims.

2. One Skilled In The Art Would Not Have Been Motivated To Modify Examples 9 and 19 Of Page As Suggested By The Examin r

The lack of motivation to arrive at the substituent at the 21- position of the claimed compounds holds true in light of the specific compounds that are disclosed in Page. The Examiner particularly emphasizes the disclosure of the compounds of Examples 9 and 19 of Page, but even concedes that the radicals at the 21-position of those compounds are hydroxyl or acetate groups, not the required -O-CO-[(C_1-C_4)-alkyl]-phenyl group. In fact, each compound of Examples 1-28, the 10 specific compounds listed in Example 29, and

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the 5 compounds utilized in Examples 30-34 all recite aliphatic group substituents in the 21-position, not the required -O-CO-[(C_1-C_4)-alkyl]-phenyl group. Following the reasoning of In re Baird, Page's disclosure of these different specific compounds, which conspicuously lack the 21- position chain used by the appellants, and do not contain any phenyl groups at all, actually teaches away from selecting the variables necessary to arrive at the present invention. See In re Baird, 29 U.S.P.Q.2d at 1552. See also MPEP § 2144.08 ("disclosure of dissimilar species can provide teaching away") (citing In re Baird).

Even if one skilled in the art would have desired to modify the compounds of Example 9 and 19, the Examiner has not explained why that person would have chosen to specifically modify the R_5 substituent of those two particular Examples, in the specific way suggested by the Examiner, while leaving all other substituents in such a way that they would approximate the corresponding substituents of the presently claimed compounds. As appellants have noted previously, one skilled in the art knows that a steroid molecule can be modified at numerous sites. In light of the above, the claimed compounds could only have been approximated from a complex hindsight selection of specific substituents from Page. Such hindsight construction of the claimed compounds may not form the basis of this rejection. See In re Fritch, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious.").

The Examiner asserts that the motivation to derive appellants' compounds may be found in Page because it allegedly teaches an equivalence between a hydroxyl group and an acyl group in the 21-position, and an equivalence between acyl groups having an alkyl and an aralkyl moiety. The Examiner's assumptions about "equivalence" between the various substituents in the Page formula appear to disregard the requirement that the art motivate the swap of substituents on the compounds. The mere theoretical possibility of selecting the compounds of Examples 9 and 19 of Page, and the theoretical possibility of modifying those compounds in the way suggested by the Examiner, is insufficient to

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support this rejection. Instead, the prior art must motivate one skilled in the art to follow the direction proposed by the Examiner. In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.").

Furthermore, the Examiner's assumptions about "equivalence" between the various substituents in the Page formula also appear to contradict the reasoning of In re Baird and In re Jones. In those decisions, the specific examples disclosed in the prior art could very well have been modified, using substituents that were disclosed as alternatives to each other in the prior art references, to arrive at the claimed compound. Even so, nothing in the generic disclosure and specific examples motivated those substitutions, rendering those disclosures insufficient to create the *prima facie* case of obviousness. Furthermore, as explained above, Page's emphasis on the dissimilar aliphatic 21-position substituents in all the disclosed examples, including Examples 9 and 19, actually acts as a teaching away from the present invention, not a teaching of equivalency.

Appellants note that the prior art as a whole likewise did not teach or suggest the modification. For this purpose, appellants refer to the teachings of all patents cited by the Examiner in the Notice of Reference Cited that accompanied the Office action dated July 25, 1995 (Paper No. 7). None of the patents teaches the 21- position substitution used by the appellants in the present claims. Two of the patents have an effective filing date subsequent to Page, and one of those even names Philip R. Page as a co-inventor. As the propriety of the Examiner's proposed modifications is determined by the teachings of the prior art as a whole, these patents are relevant to show that the state of the art did not motivate those modifications.

U.S. Patent No. 5,026,693 to Villax et al., which names Philip R. Page as a co-inventor, teaches esters of 9α-fluoro and chloro-corticosteroids having a substituent Y that corresponds to appellants' side chain in the 21- position following the CH_2 group. Y of Villax et al. can be, *inter alia*, OR_1, where R_1 may be a benzoyl group (see col. 1, lines 64

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and 65), but Y cannot be a group such as $C_6H_5CH_2$-CO- or $C_6H_5CH_2CH_2$-CO-. Therefore, no 21-phenyl carboxylates such as 21-phenyl acetates or 21-phenyl propionates are suggested, and none of the disclosed compounds suggests the modification proposed by the Examiner.

U.S. Patent No. 4,619,922 to Annen et al. teaches 6α,16α-dimethyl corticoids having a substituent Y that corresponds to appellants' side chain in the 21- position following the CH_2 group. The Y substituent of Annen et al. may be benzyloxy (see col. 1, lines 37-39) but there is no teaching or suggestion of 21-phenyl carboxylates such as 21-phenyl acetates or 21-phenyl propionates.

Having effective filing dates subsequent to Page, these patents confirm that one skilled in the art, even when in possession of the Page disclosure, would not have been motivated to arrive at the present compounds.

Likewise, a number of patents that may have effective filing dates prior to Page also would not have suggested the Examiner's proposed modifications. U.S. Patent No. 4,918,065 to Stindl et al. teaches corticoids having a substituent Z that corresponds to appellants' side chain in the 21- position following the CH_2 group. The Z substituent of Stindl et al. may be benzyloxy (see col. 1, lines 58-59) but there is no teaching or suggestion of 21-phenyl carboxylates such as 21-phenyl acetates or 21-phenyl propionates. U.S. Patent No. 4,701,451 to Annen et al. teaches 6,16-dimethylcorticoids having a substituent Y that corresponds to appellants' side chain in the 21- position following the CH_2 group. The Y substituent of Annen et al. may be benzyloxy (see col. 1, lines 40-41) but there is no teaching or suggestion of 21-phenyl carboxylates such as 21-phenyl acetates or 21-phenyl propionates.

U.S. Patent No. 4,645,763 to Annen et al. teaches 6α-methyl corticoids having a substituent X that corresponds to appellants' side chain in the 21- position following the CH_2 group. The X substituent of Annen et al. may be acyloxy (see col. 1, lines 27-28) or benzyloxy (col. 8, lines 53-54), but there is no teaching or suggestion of 21-phenyl

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carboxylates such as 21-phenyl acetates or 21-phenyl propionates. U.S. Patent No. 4,567,172 to Kamano et al. teaches 6α-methylprednisolone derivatives having a substituent -O-R^1, where R^1 may be -CO-R^3, and R^3 may be a phenyl group (see col. 2, lines 40-63). This disclosure does not teach or suggest 21-phenyl carboxylates such as 21-phenyl acetates or 21-phenyl propionates. Finally, U.S. Patent No. 4,555,507 to Annen et al. teaches 6,16-dimethylcorticoids having a substituent Y that corresponds to appellants' side chain in the 21- position following the CH_2 group. The Y substituent of Annen et al. may be benzyloxy (see col. 1, lines 38-39) but there is no teaching or suggestion of 21-phenyl carboxylates such as 21-phenyl acetates or 21-phenyl propionates.

In light of the above, the prior art as a whole would not have motivated one skilled in the art to arrive at the claimed compounds. The rejection of all the pending claims is therefore in error and should be reversed.

3. Claims 9 and 10 Are Each Separately Patentable Over The Prior Art

Claims 9, and 10 depend from claim 1 and further define the substituents A, Y, Z, (C_1-C_4)-alkyl, R(1), R(2), and R(3) in the formula I. As with the compounds of the formula I, the Page disclosure would not have motivated one skilled in the art to derive either of these two more specific compounds, because such a derivation of the compounds could only have been made by selectively choosing, in an unguided fashion, a high number of independent variables simultaneously to arrive at the compounds.

With respect to claim 9, nothing in Page would have taught or suggested the simultaneous selection of the following substituents:

X as hydrogen (instead of chlorine or fluorine);

R_1 as hydrogen (instead of fluorine, chlorine or α- or β- methyl);

R_2 as hydroxyl (instead of halogen or oxo);

R_3 as hydrogen (instead of α- or β- methyl);

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R_4 as an acyl group of the formula RCO, in which R is an aralkyl group of 7 to 8 carbon atoms (instead of R being an alkyl group containing 1 to 16 straight chained, branched, or cyclic carbon atoms and instead of a phenyl group);

R_5 as R_6 (instead of as a hydroxyl group),

R_6 as OR_7 (instead of as a hydrogen or as one or two halogen atom substituents),

R_7 as an acyl group of the formula R'CO, with R' as an aralkyl group of 7 to 8 carbon atoms (instead of R' as a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and

aralkyl group as a C_1-alkyl connected to unsubstituted phenyl.

Furthermore, one skilled in the art would not have been motivated to derive this compound in light of the compounds of Examples 9 or 19 of Page. More particularly, with respect to Example 9, Page did not suggest using hydrogen in place of fluorine in the variable X; replacing the methyl with a hydrogen in R_3; replacing the 17-valerate with -O-CO-phenyl; and replacing the 21-acetate with -O-CO-[C_1-alkyl]-phenyl. For Example 19, Page did not suggest swapping hydrogen in place of fluorine in the variable X; replacing the methyl with a hydrogen in R_3; or replacing the 21- hydroxyl with -O-CO-[C_1-alkyl]-phenyl.

With respect to claim 10, nothing in Page would have taught or suggested the simultaneous selection of the following substituents:

X as fluorine (instead of hydrogen or chlorine);

R_1 as hydrogen (instead of fluorine, chlorine or α- or β- methyl);

R_2 as hydroxyl (instead of halogen or oxo);

R_3 as β-methyl (instead of hydrogen or α-methyl);

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R_4 as an acyl group of the formula RCO, in which R is an aralkyl group of 7 to 8 carbon atoms (instead of R being an alkyl group containing 1 to 16 straight chained, branched, or cyclic carbon atoms and instead of a phenyl group);

R_5 as R_6 (instead of as a hydroxyl group),

R_6 as OR_7 (instead of as a hydrogen or as one or two halogen atom substituents),

R_7 as an acyl group of the formula R'CO, with R' as an aralkyl group of 7 to 8 carbon atoms (instead of R' as a straight, branched, or cyclic alkyl group of 1 to 16 carbon atoms and instead of a phenyl group), and

aralkyl group as a C_1-alkyl connected to unsubstituted phenyl.

Furthermore, one skilled in the art would not have been motivated to derive this compound in light of the compounds of Examples 9 or 19 of Page. More particularly, with respect to Example 9, Page did not suggest replacing the 17-valerate with -O-CO-phenyl; and replacing the 21-acetate with -O-CO-[C_1-alkyl]-phenyl. For Example 19, Page did not suggest replacing the 21- hydroxyl with -O-CO-[C_1-alkyl]-phenyl.

The rejection as it applies to claims 9 and 10 is therefore in error and should be reversed.

II. Rejection of Claims 1, 4-5, And 7-10 Under 35 U.S.C. § 103(a) Over Annen t al.

In the Office action dated November 19, 1997 (Paper No. 14), the Examiner rejected then claims 1-2 and 4-5 under 35 U.S.C. § 103(a) over U.S. Patent No. 4,645,763 to Annen et al. ("Annen") (See item 15 of the Office action). In subsequent Office actions dated June 16, 1998 (Paper No. 20), and November 5, 1998 (Paper No. 22), the Examiner neither explicitly withdrew nor specifically maintained that rejection. Appellants requested clarification from the Examiner of this rejection in the Amendment After Final, but the

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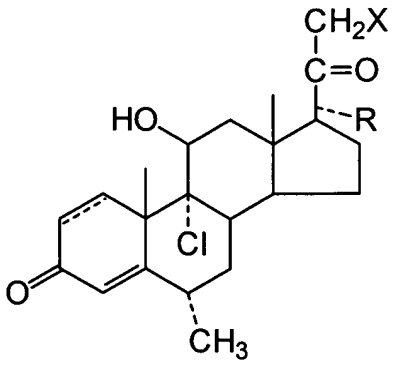
Examiner did not respond to this concern. As this rejection has not been withdrawn, appellants respond to the rejection again as follows.

Annen discloses compounds of the formula I:



I

in which the X substituent corresponds to the portion of the side chain in position 21 of the presently claimed compounds beginning with the oxygen following the CH_2 group. The X substituent of the patent can be acyloxy (see col. 1, lines 27-28) or benzyloxy (see col. 8, line 54), but there is no teaching or suggestion of a compound such as the 21-phenyl acetate or 21-phenyl propionate now included in the claims herein. For these reasons, this rejection is in error and should be reversed.

III. Rejection of Claim 7 Under 35 U.S.C. § 112, Second Paragraph

In the Office action dated November 5, 1998 (Paper No. 22), the Examiner rejected claim 7 under 35 U.S.C. § 112, second paragraph, as incomplete because it lacked a definition of R(2). The Examiner also noted that claim 7 did not end with a period. Claim 7 was amended in the Amendment After Final to correct the deficiencies noted by the Examiner, and the rejection should therefore be reversed.

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CONCLUSION

For the reasons set forth above, appellants maintain that the Examiner has not established a *prima facie* case of obviousness based on the cited documents. Accordingly, appellants respectfully request reversal of the rejection of claims 1, 4-5, and 7-10 under 35 U.S.C. § 103(a). In light of the amendment to claim 7 after final, appellants also respectfully request that the rejection of claim 7 under 35 U.S.C. § 112, second paragraph be reversed.

If there is any fee due in connection with the filing of this Appeal Brief, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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